- Food surveys combined with human biomonitoring should identify carcinogen contaminated food components, and lead to modifications in food processing/preparation to avoid heterocyclic amine formation/exposure.

3.5 Justification of proposed research

Within the frame of the mission and of the guiding principles of the Agency's activity this line of research is relevant as it addresses a common cause of cancer from the perspective of increasing the interaction between laboratory and epidemiological research: laboratory markers of tobacco-related carcinogens and of genetic determinants of carcinogen metabolism are developed for use in epidemiological studies.

4. CASE-CONTROL STUDY OF PASSIVE SMOKING AND LUNG CANCER

4.1 Participants

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4.2 Progress and achievements

4.2.1 Background

Active tobacco smoking has been established as causing cancer in the lung and other sites (for a review see, for example, IARC 1986). This effect is quantitatively related to the amount of tobacco smoked and there is no evidence that a threshold exists below which no increase in risk would occur. Environmental tobacco smoke (ETS) has similarities of composition with mainstream tobacco smoke, including the presence in it of several established

carcinogenic chemicals: this leads to the expectation that exposure to ETS should entail some increase in lung cancer risk. Support for this inference is now provided by the ensemble of results accumulated over the current decades. On one side, nonsmokers have been shown to absorb ETS products in proportion to the amount of tobacco smoked by other people in their presence (Jarvis, 1989; Riboli et al., 1990). On the other, more than 25 studies (see, e.g., Pershagen, Simonato 1991) have now directly investigated the relationship between ETS and lung cancer. The aggregate evidence from these studies indicates that, as already stated by the IARC Working Group on Tobacco Smoking (1986) "passive smoking gives rise to some risk of cancer". Quantitative estimates of the size of the ETS-related excess risk remain, however, uncertain. Under average conditions of exposure in the home environment it appears unlikely that the risk of lung cancer would exceed 50%, though it is possible that higher increases may be experienced for high or prolonged domestic exposures or by particularly susceptible subjects (comparable exposures outside the home environment, such as at work or in public places, would be expected to produce comparable increases in risk). To elucidate these important quantitative issues the IARC started in 1989, with the support of the "EUROPASS" concerted action of the European Community, a case-control study of lung cancer in lifetime nonsmokers in 11 centres in Europe, using for the assessment of exposure to ETS a questionnaire directly derived from one previously validated in an international IARC study (Riboli et al., 1990) and exploring the possible role of individual susceptibility in the development of lung cancer through the determination of several genetic biomarkers in blood lymphocytes of cases and controls. In fact, differences in individual susceptibility to lung cancer have been originally hypothesized from the obvious observation that only a minority of tobacco smokers develop lung cancer, the question being to what extent this may reflect intrinsically random events or the existence of subsets of individuals with different acquired or inborn susceptibilities. A number of cytogenetic and molecular studies have indicated as well a role for genetic predisposition to lung cancer. Variation in the ability to metabolize xenobiotics has been considered as a possible explanation for individual susceptibility and two traits have appeared in this respect particularly promising: the debrisoquine metabolism polymorphism and the arylhydrocarbon hydroxilase (AHH) polymorphism. The debrisoquine polymorphism depends on the cytochrome P450 CYP2D locus that encodes cytochrome CYP2D6. This genetic polymorphism was first identified by the reduced capacity of 5-10% of Caucasian populations to

metabolize the marker drugs debrisoquine or sparteine and has been termed the poor metabolizer phenotype. Although CYP2D6 gene has not been identified in human lung tissue, and the enzyme has not been shown to be active in the metabolism of pulmonary carcinogens, such as polycyclic aromatic hydrocarbons, it has been suggested as a host susceptibility factor for lung cancer in a number of epidemiologic studies based on the characterization of metabolic phenotype which, however, suffers some limitations (Caporaso et al., 1990). Recently, a simple DNA-based genetic assay has been developed to identify a primary mutation responsible for the metabolic defect (Gough et al., 1990).

The expression of genes within the cytochrome P450 CYP1A family has been extensively studied. It appears to be mediated by a cytosolic receptor named the aromatic hydrocarbon (Ah) receptor. P450 isozymes in the CYP1A gene family are highly active in the conversion of a variety of chemical carcinogens to their ultimate carcinogenic species, particularly cigarette smoke components such as PAHs and aromatic amines. There have been many studies to establish whether individual differences in the regulation of genes in the CYP1A gene family in humans are a factor in lung cancer susceptibility. In particular, there is evidence that the increased risk of smoking-induced lung cancer is associated with high activity of AHH, an inducibiligy phenotype of P4501A1, not only in peripheral lymphocytes (the easiest to obtain and most often commonly used test material) but also in case-control comparisons using target tissues (human lung) (Bartsch et al., 1990b). However, the overall data remain still open to discussion, primarily because individuality in CYP1A1 inducibility has not been clearly shown to be genetically determined, although some population studies reported a trimodal distribution with 10% of the population exhibiting a high inducibility phenotype.

Polymorphism is also known for other enzymes possibly involved in the metabolism of carcinogens, such as CYP2E1 and acetyltransferases. Methods to identify genotypes are being developed very rapidly, and it may be possible in 1-2 years to have available techniques other than those described above.

4.2.2 Results

(a) Estimation of magnitude of risk of lung cancer

In addition to the assessment of exposure to ETS the protocol includes an assessment of residential history, occupational history, and exposure to 35 known or suspected occupational carcinogens. A validation of the lifetime smoking history, particularly to verify misreporting of nonsmoking status, is being carried out in 8 out of 11 participating centres. The progress of the

study, as assessed at the beginning of 1992 is summarized in the table attached. Ongoing monitoring of the data collection indicates that this continues to proceed regularly and can be expected to be terminated - at the latest - by end 1993. Procedures for data quality control have been established and tested on preliminary sets of data.

(b) Genetic susceptibility to lung cancer

Collection of blood samples is ongoing in some of the collaborating centres. Samples are stored locally.

4.3 Research plans 1993-94

(a) Estimation of magnitude of risk of lung cancer

The collection of data will be completed in all participating centres by the end of 1993. As shown in the above-mentioned table, it is expected that more than 750 lung cancer cases will be eventually collected in nonsmokers, with more than 1100 controls. Data will be transferred to IARC and incorporated into a common dataset. Preliminary analysis will be started during the second half of 1993. A meeting of the collaborators will be convened at the end of 1993, to discuss the strategy for the analysis. The final analysis will be carried out in 1994. Preliminary reports will be drafted.

(b) Genetic susceptibility to lung cancer

Blood samples will be collected and stored in participating centres during 1993. They will be shipped to IARC during early 1994. Analysis will be performed in 1994.

(c) Project on active smoking and lung cancer

Alongside lung cancer cases in nonsmokers, smoking lung cancer cases and controls are enrolled in a number of centres participating in the study on passive smoking, as shown in the enclosed table. Information on smoking, residential, and occupational history is collected according to a standard questionnaire. Among the major scientific issues to be addressed are the role of time-related variables (e.g., age at start, time since quitting) in the carcinogenic effect of tobacco smoke, the effect of different types of tobacco products, the interaction between tobacco products and occupational and residential factors.

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Resources

Regular budget:

staff supported by regular budget: 18 man months

regular budget allocation: US $3 000/year

Extra budgetary funds:

EC EUROPASS project: US $110 000 (total for the 2 years)

[For project (c) a grant application for a combined analysis has been submitted by Dr L. Simonato (Veneto Tumour Registry, Padua) to the DIOMED-1 programme of the EC. Subject to the outcome of the application a combined database will be created at IARC in 1994].

4.4 Future directions 1995-96

(a) Estimation of magnitude of risk of lung cancer

(b) Genetic susceptibility to lung cancer

Reports of the case-control study on ETS and the project on susceptibility to lung cancer will be finalized for publication and the project concluded during 1995.

(c) Project on active smoking and lung cancer

Subject to the outcome of the application for funds from the Commission of the European Communities, a combined analysis of the study on active smoking will be carried out during 1995. Reports and publications will be finalized for publication and the project concluded during 1996.

4.5 Justification of proposed research

Within the frame of the mission and the guiding principles of the Agency's activity this line of research is relevant, as it aims at an accurate quantitative estimate to a widespread involuntary exposure (ETS) as well as at identifying subjects who may be particularly prone to develop lung cancer when exposed to ETS; subordinately, it may accrue quantitative information on the joint effects of tobacco smoke and occupational and residential exposures.

CENTRE	TIME		ENROLLED SUBJECTS				EXPECTED SUBJECTS AT THE END OF THE STUDY				CASES: CONTROLS RATIO		MATCH. VAR.	QUESTIONNAIRE			VALIDATION			GENETIC SUSCEPTI. STUDY
	Beg.	End	MS	MNS	FS	FNS	MS	MNS	FS	FNS	POP	HOSP		Diet	Occup.	Other	Inter. next kin	Relat. index subject	Urinary cotinine	Blood oral mucosa
Vienna	04/90	12/93	125	0	-	2	250	2	-	~15	1:1 (M)	1:2 (F)	=	+	IARC		X	-	X	X
Villejuif	10/89	12/93	-	9	90	21	-	~25	300	~55	-	1:2	S,A,DD	-	IARC		X	-	N/A	X
Bremen	01/88	12/92	570	14	80	38	~780	~20	~120	~50	1:1	-	S,A,R	-	Bremen	Family history	(X)	X	X	X
Padua	01/90	6/92	~570	8	~140	22	~680	~10	~150	~25	1:1	-	-	-	(IARC)		-	X	X	(X)
Turin *	01/91	12/92	~185	5	~45	17	~450	~102 <	~250	~40	1:3	-	S,A	-	IARC	Diesel	-	-	-	X
Barcelona	03/89	12/91	-	6	20	75	-	~10	20	~85	-	1:2	S,A,R	+	(IARC)		129	30	N/A	N/A
Oxford	04/83	6/93	~450	3	190	15	640	~5	~270	~20	c	c	S,A,R	β-car vit A	(IARC)	Radon	-	-	-	-
Lisbon	01/90	12/93	-	7	-	22	-	~25	-	~90	1:1	1:1	S,A, race	-	-	-	47	-	N/A	X
Vila Nova	01/90	12/92	-	7	-	14	-	~15	-	~28	1:1	1:1	S,A,R	-	-	-	X	X	-	X
Stockholm	11/89	11/92	-	12	-	17	-	~30	-	~30	1:2	-	S,A,R	+	IARC	Radon	18	X	(X)	X
Wuppertal	11/90	12/93	900	15	100	55	1400	22	150	80	1:1	-	S,A,R	+	Bremen	Radon, family history	-	-	-	?

* It was noted that the estimate for Turin, particularly of male non-smokers

MS: male smokers
MNS: male non smokers
FS: female smokers
FNS: female non smokers

POP: population controls
HOSP: hospital controls
SEX: sex
A: age

DD: date of diagnosis
R: residential area
*: it may be extended
N/A: not applicable

c: cases:controls ratio undetermined
X: participation
(X): possible participation